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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,724	09/08/1999	GERLINDE LENZEN	045636-5025	3497

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/319,724	LENZEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,25,26 and 29-46* is/are pending in the application.

4a) Of the above claim(s) *30-32,38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *22,25,29,33,34,36,37 and 39* is/are rejected.

7)☐ Claim(s) *23,26 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *110804*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 10/6/04, have been entered in full.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/6/04 has been entered.

Claims 30-32, 38, 40-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously.

Applicant is notified that any outstanding rejection or objection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and/or Applicant's persuasive arguments.

Regarding the status of claim 28 in the 04/06/2004 Office action, this claim was erroneously missing from the 35 U.S.C. 112, first paragraph rejections. It was not the intention to imply that the claim was allowable. It is noted that the claim has been cancelled by Applicant.

Response to Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 requires a method comprising the step of measuring an appropriate transduction signal. The specification has not taught what transduction signals are to be considered appropriate. The use of the word "appropriate" implies that there are other transduction signals that would not be appropriate, yet the specification has not asserted what transduction signals are to be considered appropriate. Therefore, an artisan could not unambiguously know whether or not he or she was practicing the claimed invention.

It is noted that this rejection had been made in the past and withdrawn, however it is reinstated after further consideration. In Applicant's response of 7/24/03, Applicant argued that several examples of how the transduction signal can be measured. This argument has been fully considered but not deemed persuasive. Examples are not sufficient to define the metes and bounds the claim. One of skill in the art would expect that a multitude of transduction signals are present in the cells used in the claimed method yet the specification has not set forth which are appropriate as demanded by the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 25, 29, 33, 34, 36, 37 and 39 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding a protein of SEQ ID NO: 14 and the portion thereof capable of binding ICYP i.e. SEQ ID NO: 1, does not reasonably provide enablement for polynucleotides that do not encode a polypeptide of SEQ ID NO: 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention as currently claimed, as set forth below.

Claim 22 requires that the "substantially pure" polypeptide comprise sites capable of binding ICYP, etc., and wherein said polypeptide mediates inhibition of eosinophil chemotaxis. The instant polypeptide is known to be an integral membrane protein, and one of skill in the art would consider it more likely than not that the substantially purified polypeptide of claim 22 could be incorporated into liposomes or micelles and be able to bind ICYP, as these types of assays are standard in the art of membrane receptor biology. Yet, one would not expect such a receptor would perform its cellular function (inhibition of eosinophil chemotaxis) in a substantially purified form, i.e. outside of the cell membrane. Although this is probably not Applicant's intention, the wording of the claim requires this and is thus not enabled.

If, however, the claim was re-worded to require that the claimed polypeptide mediate inhibition of eosinophil chemotaxis while present in the membrane of the eosinophil, then the scope of enablement issues remain i.e. there is no teaching of an assay that could identify members of the genus of variants produced that could actually mediate inhibition of eosinophil chemotaxis, and nor is one known in the art.

If the phrase "wherein said polypeptide mediates inhibition of eosinophil chemotaxis" were removed from the claim, then there would remain several issues that would demand a scope of enablement rejection. In this scenario, the function of the variants would simply be to bind ICYP etc. An assay may identify variants that merely bind ICYP etc. but the specification has not taught what to use them for.

Additionally, Claim 39 requires an assay comprising the step of measuring an appropriate signal transduction signal. The specification has provided two signals which, given the broadest reasonable interpretation, can be considered to be "signal transduction signals", e.g. eosinophil chemotaxis and colon smooth muscle segment relaxation (pages 24-27). One skilled in the art appreciates that these phenomena are presumably the endpoints of what is most probably a complex series of intracellular biochemical signals that form what is known in the art as a signal transduction cascade. Claim 39 reads on measuring any of these unknown signal transduction signals, yet the specification, as well as the state of the art at the time of filing, provides absolutely no specific information as to what these signals may be. This is true of TM9SF family members in general and the instant TM9SF-3 in particular, see the last paragraph of Sugasawa-T et al., J. Biol. Chem. 272(34)21244-21252,1997. Thus, claim 39 cannot be considered to be enabled commensurate with its scope.

The specification asserts that the polypeptides of SEQ ID NO: 1 and 14 are capable of inhibiting eosinophil chemotaxis and are useful in the study of ICYP transduction and drug development, yet the claims claim a vast genus of polypeptide variants of either SEQ ID NO: 1 or 14, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 1 or 14. Applicant has not provided sufficient guidance as to how to make and use the polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 1 or 14, but which still retain a useful property of the polypeptide of SEQ ID NO: 1 or 14. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 1 or 14 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 1 or 14 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 1 or 14, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 1 or 14

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively

conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 14 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is

dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the incalculable number of variants recited in the claims and screen same for activity, such a screen not being known in the art or taught in the specification, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Applicant argues that the claims have been amended to require the function of inhibiting eosinophil chemotaxis and that one of skill in the art could easily make and screen for proteins with the required functional attributes. This argument has been fully considered but not deemed persuasive. As set forth above, there does not appear to be a method known in the art for screening for functional variants that mediate inhibition of eosinophile chemotaxis. And, as discussed above, although binding assays are common, the specification has not taught how to use any functional variants that might be identified by such a binding assay.

Applicant's arguments regarding natural variants are persuasive, although no claim has been so limited.

Claims 22, 25, 29, 33, 34, 36, 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and reiterated below:

The specification discloses a polynucleotide of SEQ ID NO: 13 and a portion thereof SEQ ID NO: 2, yet the claims encompass polynucleotides not described in the specification, i.e. sequences from other species, mutated sequences, allelic variants, or artificial sequences that hybridize to SEQ ID NO: 13. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 13, and a single portion thereof SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence

SEQ ID NO: 13, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlations, methods of making the claimed product, or combination thereof. In this case, the only factor present in the claim is a requirement that the variants be sufficiently structurally related so that they hybridize to the reference sequences under specified conditions. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Thus, with the exception of the of the polynucleotide of SEQ ID NO: 2 and 13, and other polynucleotides which encode a polypeptide of SEQ ID NO: 1 or 14, the skilled artisan cannot envision encompassed variants. Therefore, only polynucleotides encoding a polypeptide of SEQ ID NO: 1 or 14, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

As stated previously in *Noelle v. Lederman et al.*, Interference No. 104,415, the claims in that case were directed to antibodies, the decision was based on whether or not Appellant (*Noelle*) was in possession of the protein that the antibodies would be raised against. *Noelle* had

described the murine protein and an antibody, but the claims were to a human antibody that bound to the human homolog of the murine protein. The court stated that **if** *Noelle* was in possession of the human protein, then antibodies to the human protein would be adequately described. However, the court determined that simply disclosing the murine protein did not put *Noelle* in possession of the human protein. There is no reason to think that the court would have found that *Noelle* was in possession other species variants if *Noelle* had simply described the human protein, as in the instant case. To the contrary, the court agreed with the definition of the written description requirement as set forth in *Vas-Cath*, 935 F.2d at 1563-64, and quoting *Fiers v. Revel* 984 F.2d 1164, 1170 (Fed. Cir. 1993), that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Applicant argues that the claims are not claiming a specific species but a genus. This argument has been fully considered but not deemed persuasive. As admitted by Applicant, *Noelle* was denied the genus claim as well.

Applicant argues that in contrast to *Noelle*, Applicant's have described two species and provided evidence of a high level of homology across species within the genus. This argument has been fully considered but not deemed persuasive. The court held that "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated" see p 1515 of Noelle. The evidence for a high level of

homology pointed to by Applicant in the Declaration is provided by a database search using the sequence of a small peptide of 14 amino acids known in the art to be highly conserved among all known members of the TM9SF superfamily of proteins, see page 232, col 2, middle paragraph of Sugasawa-T et al., Gene 273(227-237)2001. With the single instant exception, nothing is known about what functions members of this enigmatic family might have.

Applicant argues that *Noelle* set forth that each issue of written description must be decided on its own facts, thus the precedential value of cases in this area is extremely limited. This is not disputed by the examiner.

In Applicant's arguments (page 13) regarding the analogous relationships between the antigen (protein) and antibody of *Noelle* and the protein and DNA of the instant claims, Applicant confuses the role that each plays in the analogy. The antibody is essentially irrelevant to the instant argument. Noelle ruled that simply having the mouse protein did not put one in possession of the human protein nor of the genus of proteins. Thus, in the instant case, simply describing the human proteins does not put one in possession of proteins from other species.

Applicant's arguments regarding Example 9 of the Written description guidelines are persuasive in part, in that the claims are now constructed as to reflect an allowable claim. However, in Example 9 the specification discloses the clones were assayed for adenylate cyclase activity. The instant specification discloses no such assay for isolated clones that mediate inhibition of eosinophil chemotaxis, and nor is such known in the art. Thus to be in possession of this genus an assay must exist where by the specific function of the proteins, as specifically required by the claims, can be determined. Thus the skilled artisan would not recognize that Applicant was in possession of the claimed genus. If the phrase "wherein said polypeptide

mediates inhibition of eosinophil chemotaxis" were removed from the claim, the claim would be commensurate with Example 9, however, the enablement issues would remain as discussed above.

Allowable Subject Matter

Claims 23, 26, and 35 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Conclusion

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

January 4, 2005